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09/514,865	02/28/2000	ANTHONY P. SHUBER	EXT-036	9366

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/514,865	Applicant(s) SHUBER, ANTHONY P.	
	Examiner Sally A Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Specification/Informalities

1. The disclosure is objected to because of the following informalities:

A. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was

unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions,Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Appropriate correction is required.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for a disease wherein the disease is colon, lung, esophageal, stomach, pancreatic, bile duct, and duodenum cancer and wherein the integrity, as defined by molecular weight and length, of nucleic acids is determined from a patients stool sample comprising shed cells or cellular debris and finally identifying if the intact nucleic acids are present in a length that is greater than 200bp and with a larger molecular weight when compared to a predetermined threshold of a normal sample, does not reasonably provide enablement for screening for a disease wherein the disease is any supercolonic disease, cancer in its entirety, or a cancer selected from the group consisting of; prostate, liver, and lymphoma, or pre-cancer, or for the determination of nucleic acid integrity as a whole comprising shed cells or cellular debris from any bodily source and comprising any length.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or

unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-3 are broadly drawn to methods for screening for a disease wherein the disease is any supercolonic disease, cancer in its entirety, or a cancer selected from the group consisting of; prostate, liver, and lymphoma, or pre-cancer, wherein nucleic acid integrity is determined comprising shed cells or cellular debris from any bodily source and comprising any length. The specification teaches only a method for screening for a disease wherein the disease is colon, lung, esophageal, stomach, pancreatic, bile duct, and duodenum cancer. The specification further teaches determining the integrity, as defined by the molecular weight and length, of nucleic acids harvested from a patient's stool sample comprising shed cells or cellular debris. The specification also teaches identifying if the intact nucleic acids, following isolation from the stool are present in a length that is greater than 200bp and with an increased molecular weight when compared to a predetermined threshold of a normal sample. The specification does not teach a method of screening for any supercolonic disease. The specification only briefly alludes to, for example, inflammatory bowel syndrome and Crohn's disease in describing the invention's application as a screen for a wide range of diseases that result from genomic instability(Pg.11-12). While the specification teaches that it is the result of lacking apoptosis that the specifically named cancers, and allegedly all supercolonic diseases, may be identified by their characteristic, resulting integrity, the specification does not teach that the other "supercolonic diseases" claimed undergo the same mechanism as these cancerous examples. The specification does not teach why and how the genomic instability present in the non-cancerous disease states presents a feasible application of this screening method. It is therefore not clear, how this method could

also be used for the screening of all supercolonic diseases that are not taught to share the cancerous hallmark of lacking apoptosis but instead share only the impairment of the proper function of the gastrointestinal system and broadly genomic instability. The specification does not teach that supercolonic diseases provide for the applicability of such an assay relating to the presence or absence of apoptosis. Furthermore, the specification does not teach the method's ability to screen for all types of cancer or even prostate, liver, or lymphoma. While Table 4 in the specification teaches the results involving six of the claimed supercolonic cancers, the specification does not teach the way in which these forms of cancer or any cancer for that matter, result in stool samples comprising shed cells or cellular debris that are identifiable by their aforementioned method of screening. Although these cancers may also have resulted from a non-functioning, apoptotic mechanism, it is precipitous to teach that all cancers leave evidence of their resulting cellular integrity in the same way as colon, lung, esophageal, stomach, pancreatic, bile duct, and duodenum cancers. The specification further lacks teachings concerning the integrity of the DNA isolated from the shed cells or cellular debris. The specification not only omits teachings of the exact configuration of the DNA that characterizes its integrity, but it also does not teach how the integrity of DNA from any supercolonic disease is insured regardless of the way in which it is harvested from the patient(ie. stool, sputum, blood). The specification does not teach, for example, how a sputum sample is able to provide shed cells or cellular debris for the detection of colon cancer, lung cancer, and inflammatory bowel syndrome alike. The specification does not teach the use of a certain bodily sample for the detection of a certain supercolonic disease. In addition, the specification omits any teachings of this method's ability to define a "pre-cancerous" state. The Examples in the specification teach

the method's use of a "threshold" against which test samples are measured, but it does not teach a method with the ability to foreshadow a cancerous state, as it only provides the ability to compare the "Score" of a patient with a known cancer, to one without a cancer. The specification does not provide teachings to enable a skilled practioner of the art to differentiate a "pre-cancerous" state from that of a normal or any form of cancerous states. Lastly, the specification does not teach a method of screening for nucleic acids of any length isolated from any shed cells or cellular debris. The specification teaches amplification assays wherein fragments of "200 base pairs or more"(pg. 23) are amplified. It is taught that in the patients whose cells underwent apoptosis, aka non-cancerous cells, would not have larger fragments greater than 200 base pairs when harvested from their stool samples. The specification does not teach therefore this methods ability to determine the integrity as defined by any length, it teaches only determining fragments greater than 200 base pairs in length when compared to samples from control and cancerous populations. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the

art. With respect to the present invention, one cannot readily anticipate what methods for screening for a disease wherein the disease is any supercolonic disease, cancer in its entirety, or a cancer selected from the group consisting of; prostate, liver, and lymphoma, or pre-cancer, or for the determination of nucleic acid integrity as a whole comprising shed cells or cellular debris from any bodily source. Furthermore, with respect to the present case, such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

It is noted that during the prosecution of U.S. Patent No. 6,143,529 the claims drawn to the detection of cancer and pre-cancer by detecting DNA fragments of 200bp or more were allowed as a result of a submission of a Declaration from Inventor Anthony P. Shuber. However, affidavits or declarations, such as those under 37 CFR 1.131 and 37 CFR 1.132, filed during prosecution of another application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the original affidavit or declaration filed in the other application.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. A. Claims 1-3 are indefinite over the recitation of "supercolonic disease." The term "supercolonic disease" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes a supercolonic disease. It is unclear, eg. whether that refers to any disease of the colon, or to any disease of any organ in the vicinity of the colon, or to any disease in addition to or not including the colon,...etc. The claims should be amended to clarify what specific diseases are included in the "supercolonic disease" category.

B. Claims 1-3 are indefinite over the recitation of "integrity." The term "integrity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. It is unclear as to whether integrity refers to the length of a nucleic acid, the single or double-strandedness, the configuration, or the sequence of a nucleic acid, ...etc. The claims should be amended to clarify what exact characteristics of the nucleic acids are included in the determination of their "integrity".

C. Claims 1-3 are indefinite over the recitation of "intact," in reference to nucleic acids. The term "intact" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. It is unclear as to whether "intact nucleic acids refer to only full length nucleic acids, or to nucleic acids which do not include a mutation or translocation, or to nucleic acids of at least 200 bp, ...etc. The claims should be amended to clarify what nucleic acid configuration and composition is implied by the term "intact."

D. Claims 1-3 are indefinite over the recitation of, "predetermined threshold." The phrase "predetermined threshold" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. It is unclear as to what exactly the "predetermined threshold" refers, an exact numeric value established prior to testing from a control population that is applied to all samples, a specific value established for each of the different cell populations being tested eg. stool, sputum, blood, ...etc. The claims should be amended to clarify what the quantity and basis are of the "predetermined threshold."

E. Claims 1-3 are indefinite over the recitation of "pre-cancer." The term "pre-cancer" is not defined by claim 2, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. It is unclear whether the term encompasses benign cancers or dysplasias, or also includes normal cells. The claims should be amended to clarify what specific characteristics of the "shed cells or cellular debris" are identified in the "pre-cancer" category.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Villa et al. (Gastroenterology, 1996).

Villa et al. teach a method for screening the stool samples of patients for colorectal carcinoma, ulcerative colitis, and adenomas(1346-1353). Villa et al teach through

"Southern blot analysis of K-ras fragments on DNA from the stool," amplified by PCR, the presence of an intact 202 base pair fragment in a patient with colorectal carcinoma(Lanes 1 and 2, Figure 1B), the absence of this amplification product in a patient without colorectal carcinoma(Lane 3, Figure 1B), and a decreased amount (lower molecular weight) in patients with adenomas(Lanes 4 and 5, Figure 1B). With respect to the present invention, the specification teaches; "As shown in the Figures, each sample from a patient with cancer or adenoma was detected as a band having significantly greater intensity than the bands associated with samples from patients who did not have cancer or pre-cancer. All four cancer/adenoma patients identified using colonoscopy were correctly identified by determining the amount of amplifiable DNA 200 base pairs or greater in length...Accordingly, the amount of 200 bp or greater DNA in a sample was predictive of a patient disease status"(Example 1, Page 23, lines 7-14). It is noted that colorectal cancer, ulcerative colitis, and adenomas are considered to be supercolonic diseases. Furthermore, the method of Villa is considered to be one capable of determining the integrity of nucleic acids through the detection of their length, finding that nucleic acids with a length of 200 bp or greater are considered to be intact. In addition, the method of Villa includes a step of comparing cancerous samples to non-cancerous samples and is thereby considered to include a step of identifying intact nucleic acids in an amount greater than a "predetermined threshold." With respect to Claim 2, "adenomas" are considered by the Villa reference to be included as a "pre-cancer" since the reference notes that adenomas could develop into more "dysplastic ones progressing to carcinoma"(Villa et al, pg. 1350).

Double Patenting Rejection

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 6,143,529. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from a reference claim because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because present claims 1-3 are encompassed by the claims of U.S. Patent No. 6,143,529. That is, claims 1-33 of U.S. Patent No. 6,143,529 fall entirely within the scope of claims 1-3 of the present application. Specifically, the claims of U.S. Patent No. 6,143,529 include a method of screening in a human patient for cancer or pre-cancer by determining the amount of DNA present in a bodily excretion wherein determining the amount of DNA greater than 200bp in length. Furthermore, cancer and pre-cancer as defined by U.S. Patent No. 6,143,529 include the colorectal cancer and adenomas of the present application.

Claims 1-3 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 8, and 10-14 of copending Application No. 09/545,162. Although the conflicting claims are not identical, they are not patentably distinct from each other because they include a method of screening in a human patient for cancer or pre-cancer by determining the amount of DNA present in a bodily excretion wherein determining the amount of DNA greater than 200bp in length. Furthermore, cancer and pre-cancer as defined by Application No. 09/545,162 include the colorectal cancer and adenomas of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantai Dessau whose telephone number is (703)605-1237.

Sally Sakelaris
7/3/2002

CARLA J. MYERS
PRIMARY EXAMINER